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**U.S. High Production Volume (HPV)
Chemical Challenge Program**

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Potassium (2-ethylhexanoate) and Calcium bis(2-ethylhexanoate) Test Plan

Prepared by

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

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INTRODUCTION

Potassium and calcium 2-ethylhexanoate are salts of 2-ethylhexanoic acid (EHA). They readily dissociate to the corresponding metal cation (K^+ or Ca^{++}) and 2-ethylhexanoate anions. The carboxylic acid has a robust data base of health and environmental data and has already been reviewed in the OECD SIDS process. The metal cations in these cases are considered not to increase the overall toxicity of the molecule, and the effects of the salts are anticipated to be due primarily to the 2-EHA moiety. The OECD guidance document allows for the use of the acid data as a surrogate for the salts if the degree of dissociation is similar in the media of concern and the counter ion does not contribute any more (or less) toxicity.

HPV endpoints are fulfilled using a combination of data from the parent molecules and the acid dissociation product. The dossier for EHA is included to characterize the contribution of the carboxylic acid portion of the molecule. Robust summaries are provided for the relevant existing information for the parent molecule and the dissociation product. The data are presented in the attached Test Plan matrix (Table 2). In the case of potassium and calcium, it is anticipated that the counter ions will not contribute to increase the toxicity. The *in vivo* toxicity profile will be dominated by the acid moiety. The environmental profile will be affected by the water solubility and degree of dissociation.

METAL CARBOXYLATES CATEGORY

Sponsored Chemical Information

These compounds are sponsored by the Metal Carboxylates Coalition (The Coalition) managed by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Association Management Center. The Coalition is pleased to submit a justification, Test Plan, and Robust Summaries for the following compounds sponsored under the U.S. High Production Volume (HPV) Challenge Program.

<u>Chemical name</u>	<u>CAS#</u>
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6

Dissociation product

Hexanoic Acid, 2-Ethyl	149-57-5
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Use Patterns for Metal Carboxylates

The metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are tailored for use in different products or chemical reactions.

Potassium 2-ethylhexanoate is used as a catalyst for polyurethane systems (foams) and for unsaturated polyester resin systems (boats, shower stalls, etc.) and as a carbon black production catalyst.

Calcium 2-ethylhexanoate is used as an auxiliary drier in solvent-borne coatings and sometimes as a dispersing agent.

Dissociation Studies

Examination of the physical-chemical properties for each salt shows that these properties are quite similar for each, due to the structural similarities. Of particular importance to environmental effects and potential human health effects are the values for dissociation constant. Dissociation is a reversible process and the portion of dissociated salt present is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. The free acid anion and corresponding free metal cation are often much different than the salt (ion pair) moiety in characteristics such as solubility, adsorption, and toxicity. Accordingly, the dissociation constant is important because it determines the proportion of any specific acid or metal that is dissociated at a given pH. The proportion of dissociation, then, directly influences the behavior of the substance in the environment and bioavailability of the acid and metal constituents of metal carboxylate salts. Transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

Metal carboxylates readily dissociate in water. Dissociation studies have been conducted which indicate that significant dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the respective acid and metal to support the existing data for the salts and in the fulfillment of critical endpoints. The EHA salts are shown in Figure 2. Table 1 shows that the pKa values, 7.11 and 5.55, respectively, for the potassium and calcium salts are in the neutral range. The pKa for the free acid is 4.89. The dissociation studies presented here were conducted according to OECD Guideline 112. These values, then, predict high water solubility for the salts at environmental and physiological pH and suggest that salts will distribute similarly in the environment and have similar residence times in environmental compartments. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for both potassium and calcium 2-ethylhexanoate. This indicates that the absorption and any observed toxicity would be dependent upon the sum of the toxicities for the respective acid and metal when administered orally. More specifically, the potassium and calcium cations are not expected to increase the overall toxicity of the 2-ethylhexanoate anion, and the effects of the salts are anticipated to be due primarily to the 2-EHA moiety. The *in vivo* toxicity profile will be dominated by the acid moiety and the environmental profile will be affected by the water solubility and degree of dissociation.

Figure 1: Structure of 2-ethylhexanoic acid

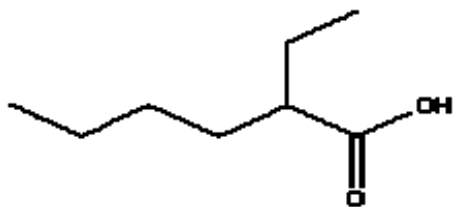
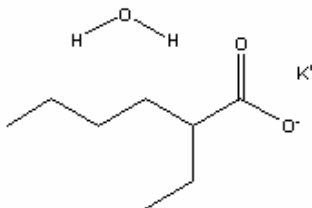


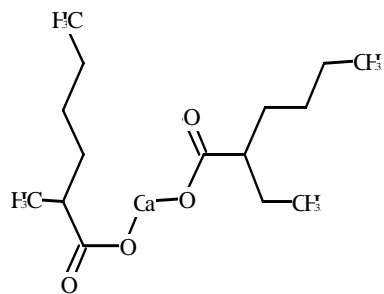
Table 1: Dissociation Constants

Chemical	CAS#	pKa Value (mean of 3)
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0	7.11 (measured & reported as pKb of 6.89)
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6	5.55 (measured as pKb of 8.45)
Hexanoic Acid, 2-Ethyl	149-57-5	4.89 (from CRC Handbook of Chemistry and Physics)

Figure 2: The structure of potassium and calcium 2-ethylhexanoate



Potassium salt



MolWt: 312.47 C15 H28 O4 Ca1
000136-51-6 Hexanoic acid, 2-ethyl-, calcium salt

The dissociation constants show that at the pH of the stomach and at the pH of environmental media the important moieties are the ionized free acid and metal. Because of this, environmental fate, ecotoxicity, and mammalian toxicity of the acid can serve as a surrogate data for the acid component of respective metal salt. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data of free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently (i.e., as the free metal and/or free acid) and one can determine the contribution of each portion of the molecule to the estimated effects.

The robust summaries for potassium EHA are in Appendix I, and those for calcium EHA are in Appendix II. These contain the data for the parent material and the estimated data for applicable endpoints when the data could be estimated from the dissociation products.

The robust summaries for 2-ethylhexanoic acid were made available to the Coalition by the American Chemistry Council Oxo Process Panel, the members of which volunteered to provide the information to the OECD SIDS program. The 2-ethylhexanoic acid data is attached as Appendix III.

Bioequivalency

The work described below by Stopford et al. (unpublished)¹ shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

Recent studies conducted to evaluate the “bioequivalency” (an estimate of bioavailability) of cobalt compounds, included three cobalt carboxylates and cobalt chloride. The solubility of these compounds in synthetic biological fluids (gastric juices, intestinal juices, several interstitial fluids, and cytosol) showed that these salts were completely dissociated and dissolved at gastric pH and cytosolic pH. The dissolution of these compounds ranged from 26.1% to 80.4 % of available cobalt at neutral pH (Table 1). The results for cobalt chloride and cobalt 2-ethyl-hexanoate were very similar at acidic and neutral pH. Cobalt neodecanoate and cobalt naphthenate showed similar levels of dissolution at acidic (gastric and cytosolic) pH, but smaller proportions of the metal component of these compounds were dissolved at neutral pH. The differences in dissolution for these metal carboxylates at neutral pH in synthetic body fluids could be related to differences in their dissociation constants.

These data are valuable in understanding the calcium and potassium 2-ethylhexanoates for three reasons:

¹ Stopford, W., J. Turner, D. Cappellini, and T. Brock. (unpublished) Bioequivalency Testing of Cobalt Compounds (Oct 15, 2002 Draft). Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute, Research Triangle Park, N.C.

1. They confirm the prediction that these compounds would be expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable at neutral pH (7.4).
2. The fraction of the three cobalt carboxylates that is dissolved at acidic and neutral pH is very similar for different acid constituents with a range of molecular weights and chain lengths. This finding greatly strengthens the extrapolation of the results to the calcium and potassium 2-ethylhexanoates.
3. The work by Stopford et al. (unpublished) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

Summary

In summary, the key points relative to the potassium and calcium salts of 2-ethylhexanoate evaluation are:

- The dissociation constants (pKa) are in the approximately neutral range;
 - Complete or nearly complete dissociation at gastric and cytosolic pH levels;
 - A moderate to high proportion of dissociation in the environmental pH range;
- Bioequivalency of salts to that of the metal cation and acid anion is assumed.

Physical chemical property data are provided for the parent molecule. The effects data for the acid dissociation product is applied to these salts.

Proposed Test Plan

The existing data for the metal carboxylate salts have been summarized in robust summaries and ranked for reliability according to EPA Guidance.

Available data are summarized in Table 2. In addition to the data available for the salt there is a complete set of robust summaries for the acid, 2-ethylhexanoic acid, which has already been assessed in the OECD SIDS program. Summaries of available data for the calcium (Ca++) and potassium (K+) ions are not provided.

Environmental Fate Parameters:

Physical chemical properties information have been developed for the EHA salts. Biodegradation will depend primarily on the free acid. Since the 2-ethylhexanoic acid has reliable biodegradation data, the Coalition will rely upon data for the acid to characterize the degradability of these EHA salts.

Ecotoxicity:

Reliable ecotoxicity data are available for the 2-ethylhexanoic acid. Since these materials dissociate at environmental pH, the data for the acid should be applicable to these salts.

Human Health Effects:

Since the molecule is essentially completely dissociated at stomach pH, the use of the data from the health effects studies for the acid should adequately characterize these salts.

Table 2 . Available and Estimated Data for 2-ethylhexanoic acid and the potassium and calcium salts

Chemical	Potassium 2-Ethylhexanoate	2-Ethylhexanoic Acid (2-EHA)	Calcium 2-Ethylhexanoate
Physical/Chemical Properties			
CAS#	3164-85-0	149-57-5	136-51-6
Molecular weight	181.31	144.2	326.5
Melting Point	355.9 C	37.72 C (MPBPWIN) < -60 C (SIAR)	ca. 160 C (Ulmann) 116.1 C (MPBPWIN)
Boiling Point	> 400 C	234.2 C (MPBPWIN) 226 – 229 C (SIAR)	403.4 C (MPBPWIN)
Vapor Pressure mm Hg	1.35 E-9 @ 25C (MPBPWIN)	.0626 (MPBPWIN)	8.65 E-7 (MPBPWIN)
Partition Coefficient (log Pow)	-0.8511 (EPI v3.11)	~ 3 (calculated) 2.64 @25C (SIAR)	3.88 (EPI v 3.11)
Water Solubility	> 10,000 mg/l	25 mg/L at 25°C	5.06 mg/l* (EPI v 3.11)
Photodegradation	t ½ = 1.680 days* (EPI v3.11)	t ½ = 1.308 days* (EPI v3.11)	t ½ = 0.937 days* (EPI v3.11)
Stability in water	pKb 6.89 @ 20C pKa = 7.11 @ 20 C	pKa 4.89	PKb 8.45 @ 20 C PKa = 5.55 @ 20C
Biodegradation	Anticipated to be biodegradable based on data for 2-EHA, and low toxicity of K ⁺	BOD ₂₀ = 83% of ThOD	Anticipated to be biodegradable based on data for 2-EHA, and low toxicity of Ca ⁺⁺
Environ. Transport %	Air 7.25E-06 Water 38.9	Air 5.29 Water 41.6	Air 1.15 Water 31.7
EPIWIN Level III Fugacity Model	Soil 61 Sediment 0.0713	Soil 53 Sediment 0.2	Soil 65.5 Sediment 1.61
Environmental Effects2			
Acute Fish: 96 hr LC50	LC ₅₀ ≥ 70 mg/L estimated based on data for 2-EHA	LC ₅₀ = 70 mg/L after 96 hours at a pH of 5.3-5.5	LC ₅₀ ≥ 70 mg/L estimated based on data for 2-EHA
Acute Daphnid 48 hr EC50	EC50 ≥ 85.38 estimated based on data for 2-EHA	48 hr EC ₅₀ = 85.38 mg/L (slightly toxic),	EC50 ≥ 85.38 estimated based on data for 2-EHA
Algae 72 hr EC50	96 hr EbC ₅₀ ≥ 40.616	96 hr EbC ₅₀ = 40.616	96 hr EbC ₅₀

	mg/L 96 hr EuC ₅₀ ≥ 44.390 mg/L estimated based on data for 2-EHA	mg/L 96 hr EuC ₅₀ = 44.390 mg/L	≥40.616 mg/L 96 hr EuC ₅₀ ≥ 44.390 mg/L estimated based on data for 2-EHA
Health Effects			
Rat Acute oral LD50	LD ₅₀ = 1600 - 3200 mg/kg; estimated based on data for 2- EHA	LD ₅₀ = 1600 - 3200 mg/kg	LD50 > 5000 mg/Kg of calcium salt.
Repeat Dose 90 day oral	Rat dietary, NOAEL = 0.5% in the diet (~ 300 mg/kg/day). NOEL = 0.1% in the diet (approximately 65 mg/kg/day). All toxicity was reversible within 28 days. Estimated based on data for 2- EHA	Rat dietary, NOAEL = 0.5% in the diet (~ 300 mg/kg/day). NOEL = 0.1% in the diet (approximately 65 mg/kg/day). All toxicity was reversible within 28 days.	Rat dietary, NOAEL = 0.5% in the diet (~ 300 mg/kg/day). NOEL = 0.1% in the diet (approximately 65 mg/kg/day). All toxicity was reversible within 28 days. Estimated based on data for 2-EHA
Genotoxicity (<i>In Vitro</i>) Bacterial - Ames Test	Not mutagenic; estimated based on data for 2-EHA	Not mutagenic	Not mutagenic
Genotoxicity (<i>In Vitro</i>) Mammalian	Not required, based on results of in vivo testing	Not clastogenic, based on in vivo testing of 2- ethylhexanol. The data from 2- ethylhexanol is directly applicable to the assessment of this endpoint for 2- ethylhexanoic acid due to the extensive metabolism of the former to the latter in vivo.	Not required, based on results of in vivo testing
Genotoxicity in vivo	not clastogenic – estimated based on data for 2-EHA	Not clastogenic - mouse micronucleus test	not clastogenic – estimated based on data for 2-EHA
Reproductive		Equivocal reproductive findings were observed in male rats at 600 mg/kg/day. Rat, 1 –generation reproduction test; NOEL for P generation: 300 mg/kg NOEL for F1 generation: 100 mg/kg	

Developmental toxicity	NOEL > 100 mg/kg estimated based on data for 2-EHA	Several studies have demonstrated that high oral doses of 2-EHA can cause developmental toxicity in rats and mice, but not in rabbits. Rat, oral, NOEL for maternal animals = 300 mg/kg/day NOEL for offspring = 100 mg/kg/day	NOEL > 100 mg/kg estimated based on data for 2-EHA
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*Modeling may not be appropriate as this material dissociates.

SUMMARY

The Test Plan reflects the combined use of salt and dissociation product data to address the HPV data elements. No additional testing is proposed for these materials.